What the first 10,000 patients with chronic urticaria have taught me: A personal journey

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Chronic urticaria remains one of the disorders treated by allergists with which there is (and has been throughout my lifetime) associated myths regarding the cause of the disorder and its treatment that are extremely difficult to dispel. In this brief article I would like to address some of these beliefs, review the literature where it exists, point out where there are gaps in our understanding, and convey some of my own conclusions that will, hopefully, become hypotheses for future investigation. Table I lists the beliefs that I think are false and potentially detrimental to the care of patients. I will expand on each of these.

I became board certified in allergy and clinical immunology in 1974, and that was a period in which chronic urticaria was seriously considered by many to be an emotional disorder.[1,2] The idea remains prominent within the public at large, leading to questions asked by many new patients, such as "Is it my nerves?" *Factitious urticaria* is another term for dermatographism, which implies that the skin reaction is not real or that the patient self-inflicts the rash and has only himself or herself to blame. It does not acknowledge the severe pruritus associated with a functional skin abnormality (yet to be defined) of cutaneous mast cells as the underlying problem. Angioneurotic edema is now just angioedema as we move away from a psychic cause of these things. The discovery of C1 esterase inhibitor deficiency as the defect in hereditary angio(neurotic)edema was particularly helpful.

Foods and food additives as a putative cause of chronic urticaria date almost as far back as "nerves" as a cause. I will mention one in particular. James and Warin[3] described exacerbations of urticaria after challenge with food yeasts and *Candida albicans* extracts; 69% of patients with a positive skin prick test response to *C albicans* had a positive challenge result to food yeast, and a "large percentage" responded to a low-yeast diet. At the National Institutes of Health (1978-1987), some of our first observations disproved this thesis by limiting foods to a diet of rice, lamb, and water for 5 days and recording the effect on the person's urticaria. The study was neither controlled nor blinded. Nevertheless, no one improved, and after the first 20 patients, we stopped. I assumed that chronic urticaria was not caused by food allergy or by uncharacterized reactions to food additives and have never become suspicious that this could be incorrect. By 1980, it was concluded that food additives precipitate hives in 2000 of 6600 patients with chronic urticaria, and one author added that reactions in asthmatic subjects are even higher.[4] As the decades passed, the reader will note that IgE-mediated food allergy is no longer considered to be a cause of chronic urticaria. Even considerations such as hives caused by benzoates,[5] aspirin and natural salicylates,[6] or yellow dye no. 5 are uncommonly seen. But the idea has now morphed into the realm of "pseudoallergy."[7] Here well-defined chemicals are claimed to cause or exacerbate the symptoms of chronic urticaria. IgE antibody is not necessary, although the mechanism or mechanisms responsible have not been discerned. Pseudoallergens include artificial food dyes, preservatives, and sweeteners, aromatic compounds in wine, tomatoes, and spices[8]; as well as phenols, such as D-hydroxy benzoic acid, citrus and orange oil, and salicylates.[9] The remission rate attributed to elimination diets varies from 30% to 90%, yet double-blind, placebo-controlled food challenges with these substances have failed to reproduce urticaria,[10] and patients whose chronic urticaria has remitted can eat anything without becoming symptomatic. The right conclusion is that foods or additives do not contribute to the pathogenesis of chronic urticaria.

Infectious processes as a cause of chronic urticaria have been considered in the past but not so prominently until the discovery of *Helicobacter pylori*. Soon thereafter, articles began to appear relating the presence of the organism to chronic urticaria or reporting effective treatment of chronic urticaria by using therapy to eradicate the organism.[11] However, other articles are negative.[12] The problem lies in the fact that the presence of the organism far exceeds the prevalence of chronic urticaria (0.5% to 1.5%)[13] and that properly controlled studies involving large numbers of patients have not been done.[14] I have seen perhaps 500 patients with chronic urticaria who have negative test results for *H pylori* and about 50 who have the organism but in whom treatment directed to it failed. Of course, the successes are not referred to me. Nevertheless, I have never ordered the test, and see no reason to do so. If one waits long enough, this idea will disappear.

Currently, the major ideas concerning the cause, pathogenesis, or both of chronic urticaria are based on observations suggesting that it has an autoimmune cause in 40% to 45% of patients. There is the association with antithyroid antibodies,[15,16] which appear to be a marker of autoimmunity[16]; the pathogenic antibodies are IgG anti-IgE receptor[17-19] or IgG anti-IgE.[20,21] The IgG antibodies activate the classical complement cascade,[19,22] and purification of IgG subclasses demonstrated histamine-releasing activity predominantly within subclasses 1 and 3.[23] If correct, future studies

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TABLE I. Myths about the cause and treatment of chronic urticaria

Myths about cause
1. Chronic urticaria is a psychosomatic disorder, with hives as a cutaneous manifestation of an emotional problem.
2. Chronic urticaria is caused by food additives or is exacerbated by pseudoallergens contained in foods.
3. *Helicobacter pylori* causes hives.
Myths about treatment
1. Nonsedating antihistamines in recommended doses are as efficacious as sedating antihistamines with much less toxicity.
2. Data demonstrating sedation with antihistamines as tested in healthy subjects or patients with allergic rhinitis can be extrapolated to the treatment of chronic urticaria.
3. Thyroid hormone can be used to treat chronic urticaria if thyroid antibodies are present.

will elucidate the mechanistic details further, which might lead to new approaches regarding therapy. If the relationship is spurious, other explanations for the presence of these autoantibodies will be found. It is clear that binding methods, such as ELISA, are not reliable for detection of these antibodies[23] and that functional assays, such as basophil histamine release or perhaps activation markers on basophils, are essential. There are also reports of basophil hyporesponsiveness[24-26] or even hyperresponsiveness[27] in subgroups of patients with chronic urticaria, and this approach might define additional abnormalities related to the cause/pathogenesis of patients who are still considered to be "idiopathic." Vonakis et al[26] found increased cytoplasmic phosphatases (Src homology domain 2–containing inositol phosphatase) as a possible explanation for diminished basophil histamine release on stimulation with anti-IgE. Decreased responsiveness, however, might be a consequence of having urticaria rather than its cause.

However, a second focus of this narrative is to present commonly believed concepts that I think are false and that lower the success rate in the treatment of patients with chronic urticaria. The most egregious is the current approach of using antihistamines. My first note of it began at the National Institutes of Health in the mid-1970s. Nonsedating antihistamines entered the market, and it made sense to try them in patients with chronic urticaria. The drugs of choice at that time were hydroxyzine and diphenhydramine, and most of our patients required 4 times daily dosing with either 25- or 50-mg tablets. This was standard practice at the time; sedation was not of particular concern. Once I switched to the nonsedating antihistamines that were marketed first (terfenadine and loratadine), I lost the ability to treat patients other than those with mild urticaria, even if I doubled the dose. During the next 20 years, articles appeared demonstrating significant improvement of symptoms in patients with chronic urticaria using most available nonsedating antihistamines. Nevertheless, from 1980 to 2008, at least 75% of patients in my practice in whom treatment with nonsedating antihistamines failed could have their symptoms managed with hydroxyzine or diphenhydramine taken round-the-clock without addition of other agents. This has never been formally studied. The only article reporting multiple daily doses of hydroxyzine at 25 mg 3 times daily suggest that it is no better than 10 mg of cetirizine.[28] Because 10 mg cetirizine equals about 30 mg of hydroxyzine, this dose of hydroxyzine might not be much better than cetirizine taken twice daily; nevertheless, the hydroxyzine dose is too low to achieve the effects of which I speak.

Is there a dose response of antihistamine effect as the dose is increased? Because antihistamines are inverse agonists that bind to the H1 receptor to shift its conformation to an inactive mode,[29] their effectiveness will depend on the percentage occupancy of the H1 receptor. This in turn relates to the amount of histamine present because histamine binds to the same receptor to shift its conformation to an active mode. The variables are the molar amounts of antihistamine versus histamine present at the skin site and the binding affinity of each. The first test of this concept was our clinical observations in treating dermatographism. This is the most purely histamine-dependent form of urticaria, and not only can we stop pruritus and induced lesions with hydroxyzine or diphenhydramine in patients in whom nonsedating antihistamine treatment fails, we can also dose-response the effect between 50 and 200 mg hydroxyzine so that control of symptoms is proportional to the dose used. This is an important observation because dermatographism cannot be treated with corticosteroids. The same effect was demonstrated experimentally using intradermal injections of histamine at 3 doses tested before and after antihistamine therapy: 0.1, 2.5, and 5 mg/mL. I was the patient, and a nurse recorded the results. The wheal-and-flare reaction was measured at baseline and after 1 week of 180 mg of fexofenadine. A prominent decrease in reactivity was noted, but all 3 doses are still 4+ by using the usual methods for reading intradermal skin tests. I then added 2 cetirizine tablets (taken in the morning and at dinner time) to the morning fexofenadine for a week and repeated the skin tests. A further decrease in wheal diameter and pruritus index was noted, and the cutaneous response to the 3 doses was 4+, 2+, and 1+, respectively. I did not appreciate any sedation. I then ingested 50 mg of hydroxyzine 4 times daily for 1 week, and when the test was repeated, there was no pruritus and the highest histamine dose was "trace positive" (ie, less than 1+). Sedation was present up to day 4, and thereafter I was unaware of any. Chronic urticaria is far more complex, but histamine release is certainly important, and my thesis is that antihistamine therapy be maximized before adding any other more toxic agent. Thus I adapted use of hydroxyzine or diphenhydramine for chronic urticaria (idiopathic or autoimmune) based on observations such as these because there are no studies of long-term antihistamine therapy in patients with chronic urticaria on which one can rely.

When antihistamines fail, the options available include corticosteroids, cyclosporine, intravenous gamma globulin, methotrexate, sulfasalazine, dapsone, hydroxychloroquine, colchicine, and cytoxan. The literature on most of these (1990 to the present) has been recently reviewed.[30] Studies of relatively small numbers of patients suggest the efficacy of each of these in occasional subjects (excluding corticosteroids and cyclosporine), but the data are insufficient to recommend them. An example is a recent study of sulfasalazine that has no placebo control.[31] Dapsone, hydroxychloroquine, and colchicine are, in my view, ineffective, but more important is that the data in support of their use are based primarily on uncontrolled studies of small numbers of patients.[32-34] The choice of these agents might be based on their apparent efficacy for urticarial vasculitis or other neutrophil-dependent dermatologic conditions. Cytoxan is very toxic, and therefore I will

focus on steroid use, which is the most common alternative used by physicians referring patients to me, and cyclosporine, which really works.[35,36] The key to effective therapy, however, is defining what is refractoriness to antihistamines. When a double dose of a nonsedating antihistamine fails to adequately alleviate symptoms or affect quality of life, we use hydroxyzine at 25 to 50 mg 4 times daily and resort to the aforementioned agents only when this fails. The number of patients presenting with steroid toxicity (obesity, hypertension, diabetes, and steroid myopathy) who can be weaned off steroids on substituting hydroxyzine for nonsedating antihistamines is at least 75%; the remainder are tapered to a reasonable dose (not >15 mg/d), and cyclosporine is added. Steroid is then tapered by 1 mg every week. The most useful double-blind, placebo-controlled study that could be done is to test the efficiency of hydroxyzine at 50 mg 4 times daily versus 10 mg of cetirizine twice daily or 5 mg of levocetirizine twice daily as the primary treatment of severe chronic urticaria.

This recommendation would, however, now be considered extreme. But why? Sedation! This concern is emphasized by the manufacturers of nonsedating antihistamines as they relate to the treatment of allergic rhinitis, and numerous studies attest to the sedation associated with first-generation antihistamines,[37-41] including one likening the adverse effect of 50 mg of diphenhydramine on driving performance to that seen with alcohol.[37] It is important to note that most other similar reports examine the effects of a single 50-mg dose of diphenhydramine in healthy individuals. Nevertheless, not all studies or reviews of these data agree.[42-44] One study compared 50 mg of diphenhydramine 3 times daily with 10 mg of cetirizine once daily for 3 consecutive days and found diphenhydramine to be more impairing on day 1, as assessed based on sleep latency (sleepiness) and a simulated assembly-line task, but the difference was gone by day 3.[42] This is what we find in patients with chronic urticaria. A second study,[44] a double-blind, placebo-controlled study of driving performance, compared a single dose of diphenhydramine (50 mg) with 5 mg of levocetirizine or placebo given for 4 consecutive days. There was no difference when levocetirizine was compared with placebo, but diphenhydramine adversely affected performance at all time points. Performance on day 4 improved relative to that on days 1 or 2 but did not match that seen with levocetirizine or placebo. However, the 95% CI for diphenhydramine at day 4 compared with day 2 indicated a change from "clinically relevant driving impairment" to "within acceptance range." Furthermore, a meta-analysis of sedation and performance impairment of diphenhydramine and second-generation antihistamines provided an equivocal answer. To quote from the report by Bender et al[43]: "A clear and consistent distinction between sedating and non-sedating antihistamines does not exist."[43] There are, however, additional objections when considering antihistamine use in patients with chronic urticaria, as follows:

1. No sedation studies have ever been done with patients with chronic urticaria. Their baseline performance is not likely to be "normal." In fact, those who are sleepless because of pruritus might perform better with approaches that include first-generation drugs.
2. Any sedation that might be seen is not comparable with the side effects of corticosteroids or cyclosporine.
3. A dose response with increasing antihistamine dosage is not considered, but one can readily demonstrate that severe dermatographism will respond to increasing amounts of antihistamines beyond the approved dosage. Likewise, for other forms of chronic urticaria, it is assumed that H1 receptors are "blocked" when the amount of histamine present might preclude that.
4. It is assumed that sedation to one 50-mg tablet will proportionately increase as the dose is increased. This is not possible based on our experience. Also, the reverse seems to be so. Taking it round-the-clock (preferable to a megadose at bedtime) leads to tolerance (ie, a perception that sedation is diminished to a tolerable level). Whether performance is really affected needs to be tested after 2 weeks of therapy and not after a few hours or even 1 to 2 days. I discontinued first-generation antihistamines in about 2% of the 10,000 patients treated because of sedation; the remainder had no complaints, and I know of no serious automobile accidents.

I think chronic urticaria is pretty easy to treat, even if severe.[45] A summary of my approach emphasizes the following concepts.

1. First use a single or double dose of any nonsedating antihistamine first. If it fails….
2. Then use increased doses of hydroxyzine starting at no less than 25 mg 4 times daily and increasing to no more than 50 mg 4 times daily. If successful, nothing else is needed, and the dose can be slowly tapered. If unsuccessful, addition of H2 receptor antagonists, a leukotriene antagonist, or both is often advocated, but the expectation of success is low. In the future, I will eliminate use of leukotriene antagonists unless new data are forthcoming and will use H2 antagonists primarily for control of gastric acid secretion when corticosteroids are used.
3. Steroids can be used for antihistamine failures but no more than 10 mg/d or 20 to 25 mg every other day with tapering, as described previously.[45] If higher doses are considered for regular use beyond this range, the drug should not be used at all. The problems with corticosteroid use in patients with chronic urticaria are due to inappropriate prescribing practices beyond the intrinsic adverse effects of the drug. Before the advent of cyclosporine, low-dose corticosteroids were often the only approach that offered relief and could be safely used for periods of up to 2 years if the above caveat is followed. Yet some of the worst cases of steroid side effects we have seen were patients with chronic urticaria being treated with 30 to 60 mg of prednisone per day for many months (eg, weight gain of 50-120 lbs, steroid myopathy that precluded ambulation, striae from the neck to the knees, and insulin-dependent diabetes).
4. Cyclosporine is an alternative to corticosteroids or can be used when steroids are unsatisfactory (nonresponse or excessive requirement for control). The adult dose is 200 to 300 mg/d. Monitoring blood pressure and blood urea nitrogen and creatinine levels every 6 weeks is essential. Blood cyclosporine levels can be checked to assist in dose adjustment.
5. Methotrexate or intravenous gamma globulin can be reserved for cyclosporine failures, for which they occasionally work. Other agents listed above are useless; agents such as hydroxychloroquine, dapsone, and colchicine can be reserved for urticarial vasculitis (about 1% of patients). Sulfasalazine needs further study with larger numbers of patients, including a control group.

It is important to note that first-generation antihistamines have additional functions that contribute to some of the side effects observed but might also contribute to the therapeutic effects observed. Those include antimuscarinic activity, anti–α-adrenergic effects, antiserotonin activity, inhibition of basophil degranulation, and activity against histamine H4 receptors that contribute to pruritus and eosinophil chemotaxis.[46] Dose adjustment is required for children, and particular caution is needed in the elderly.

Guidelines have been published for the treatment of chronic urticaria (idiopathic or autoimmune).[47,48] I reviewed them before publication and consider them to be reasonable but not optimal. Use of sedating antihistamines is viewed as extreme, use of any corticosteroid chronically is deplored, and the efficacy of cyclosporine is underestimated. Although these guidelines do not comment on the use of thyroid hormone as a treatment for subjects with euthyroid whose sera test positive for antithyroid antibodies, articles have appeared suggesting that this might be efficacious,[49] but the studies are uncontrolled and anecdotal, and a more recent guideline does not mention thyroid hormone therapy as an option.[30] Certainly there is little to suggest thyroid disease as a cause of chronic urticaria or, for that matter, urticaria as a cause of thyroid disease. Thus therapy for one disorder is not likely to affect the other. I have therefore added thyroid hormone therapy to Table I as a myth and await a large enough properly controlled study that might actually answer the question.

Before the advent of cyclosporine, steroids were overused (too much for too long) or underused (patients with severe disease were filing for disability who did not need to do so). Currently, steroids are frequently used chronically for difficult-to-treat patients, often with excessive and variable dosing, sometimes with patients self-medicating based on perceived need, and always with adverse consequences. Now we can do much better, and new approaches, such as omalizumab, are on the horizon.[50,51]

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